Toxicology of DNA Based Therapies

DNA based therapies are currently being developed for the treatment of a wide range of human diseases. Examples include plasmid DNA encoding one or more antigenic proteins for vaccines against viral and bacterial pathogens, and viral vectors for gene therapy. Although these therapies show significant promise, by their very nature all pose a risk of interacting with the host genome or disrupting normal cellular processes in unexpected and unpredictable ways with potentially adverse consequences. Therefore, it is essential to identify hazards and potential risks associated with these therapies prior to widespread clinical application. The potential for DNA based therapies to persist makes evaluation of long-term safety a top priority.

In the first successful treatment of a human disease with gene therapy (Cavazzana-Calvo et al, Science 2000, 288: 669-671), a full correction of SCID-X1 was reported in a trial that involved transduction of bone marrow cells (CD34+) with a retroviral vector carrying a transgene encoding the human common gamma chain (γc), a component of certain cytokine receptors. However, by 2002, two of the ten infants enrolled in the trial had developed T-cell leukemia, which subsequently was shown to be associated with genomic insertion of the retroviral vector (insertional mutagenesis). This adverse outcome has resulted in recent efforts to improve the safety of viral vectors. At present, the NTP is involved in collaborative studies with the FDA and other NIH institutes to develop test systems to evaluate the safety of various vectors. This presentation will describe results obtained to date and outline currently ongoing studies.